

## How to Interpret and Pursue an Abnormal Prothrombin Time, Activated Partial Thromboplastin Time, and Bleeding Time in Adults

ARIF H. KAMAL, MD; AYALEW TEFFERI, MD; AND RAJIV K. PRUTHI, MBBS

The prothrombin time (PT) and activated partial thromboplastin time (APTT) are among the most commonly ordered coagulation tests. In 2005, more than 140,000 PT and more than 95,000 APTT tests were performed at Mayo Clinic. The most common indications for ordering these tests include anticoagulant monitoring, initial evaluation of hemorrhage, and, although not generally indicated, routine preoperative screening. In addition, the bleeding time (BT) test, which is infrequently performed, is still available in certain institutions. Abnormal results from these tests (prolonged PT, APTT, and BT), especially from tests conducted for initial evaluation of hemorrhage or for preoperative screening, may pose a diagnostic dilemma to the non-hematologist. We review the essential factors affecting test results; provide a practical approach to the evaluation of a prolonged PT, APTT, and BT; and offer suggestions on which reflexive tests are appropriate and when to consider a subspecialty consultation.

*Mayo Clin Proc.* 2007;82(7):864-873

APTT = activated partial thromboplastin time; BT = bleeding time; HMWK = high-molecular-weight kininogen; INR = international normalized ratio; ISI = international sensitivity index; LAC = lupus anticoagulant; PK = prekallikrein; PT = prothrombin time; TT = thrombin time

The prothrombin time (PT), activated partial thromboplastin time (APTT), and bleeding time (BT) are screening tests for hemostasis. Typical indications for ordering these tests include hemorrhagic symptoms, monitoring of anticoagulant therapy, and “routine” preoperative screening. In 2005, more than 140,000 PT and more than 95,000 APTT tests were performed at Mayo Clinic, whereas the frequency of BT tests significantly declined. Besides the expected prolongations of the PT and APTT in patients receiving anticoagulant therapy, abnormal test results in patients with or without symptoms warrant further investigation for an underlying acquired or congenital bleeding disorder, especially if the patient is scheduled to undergo surgery. We provide an overview of hemostasis and review the approach to a patient with a prolonged PT and/or APTT and a prolonged BT.

### OVERVIEW OF THE HEMOSTATIC SYSTEM

A basic understanding of the hemostatic system, which has been reviewed in detail,<sup>1</sup> is required to interpret screening coagulation test results. When platelets and clotting factors circulate in an inactive form, blood flows freely through the

vascular system. However, vascular injury and the resulting disruption of the endothelium lead to the initiation of a complex hemostatic response broadly classified into primary and secondary hemostatic responses. In primary hemostasis, vascular injury results in (1) vasospasm; (2) endothelial disruption and exposure of subendothelial collagen, leading to platelet adhesion mediated by von Willebrand factor; and (3) platelet activation and aggregation, leading to platelet plug formation. In secondary hemostasis, the subendothelial tissue factor is simultaneously exposed, leading to the activation of the procoagulant cascade and the eventual formation of a hemostatic fibrin clot.

Bleeding disorders can be broadly classified into primary and secondary hemostatic defects. Primary hemostatic defects include disorders of platelets and von Willebrand factor, whereas secondary hemostatic defects are coagulation factor deficiencies that can be congenital or acquired.

Bleeding symptoms in the patient or in a member of the patient’s family can often prompt laboratory evaluation to test for bleeding disorders. To screen for bleeding disorders and to distinguish between congenital and acquired disorders, physicians should obtain a detailed personal and family (hemostatic) history and perform a thorough physical examination. Spontaneous bleeding (epistaxis, ease of bruising, joint bleeding) or unusual or unexpected bleeding after surgery (including dental extractions) makes it more likely that the patient has a bleeding disorder. That likelihood increases if the patient has a family history of a bleeding disorder.

If the hemostatic history raises concern for a bleeding disorder, the next step is to order screening tests for hemostasis with appropriate follow-up (reflexive) testing as indicated. Ordering screening or diagnostic hemostatic tests before obtaining a thorough patient history is not an appropriate approach.

From the Department of Internal Medicine (A.H.K.) and Division of Hematology (A.T., R.K.P.), Mayo Clinic, Rochester, Minn.

A question-and-answer section appears at the end of this article.

Address reprint requests and correspondence to Rajiv K. Pruthi, MBBS, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (e-mail: pruthi.rajiv@mayo.edu).

© 2007 Mayo Foundation for Medical Education and Research

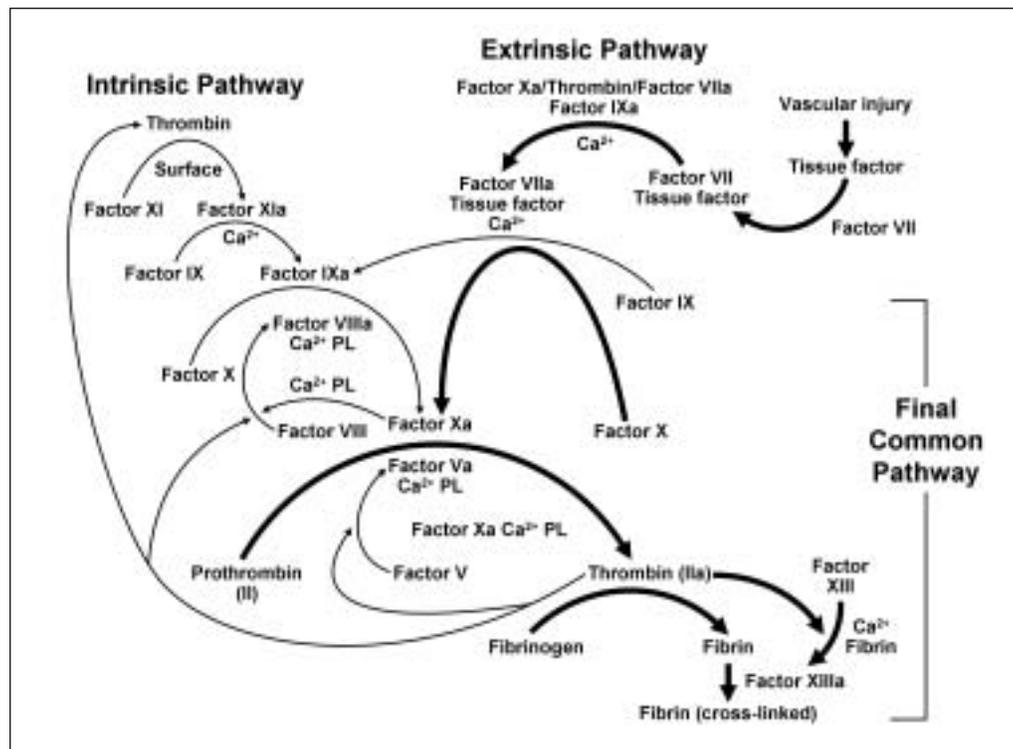


FIGURE 1. Coagulation cascade. a = activated factor; Ca = calcium; PL = phospholipid. Adapted from *Biochemistry*,<sup>2</sup> with permission from American Chemical Society, copyright 1991.

### SCREENING TESTS FOR HEMOSTASIS

The PT, APTT, and BT are screening tests for hemostasis. The BT test has lost favor in recent years, but the PT and APTT remain the most frequently ordered tests in coagulation medicine. To properly manage patients, physicians must determine whether the prolonged PT, APTT, and BT are artifactual, medication related, or representative of hemostatic abnormalities.

#### PROTHROMBIN TIME (INTERNATIONAL NORMALIZED RATIO)

Stated simply, the PT is a measure of the integrity of the extrinsic and final common pathways of the procoagulant cascade. The PT represents the time, in seconds, for patient plasma to clot after the addition of calcium and an activator of the extrinsic pathway (thromboplastin) (Figure 1). Thus, deficiencies or inhibitors of clotting factors within the extrinsic and final common pathways result in prolongation of the PT (Figure 2). Monitoring warfarin anticoagulation is the most common indication for PT. However, PT results for identical patient samples can vary with the laboratory, making monitoring of warfarin anticoagulation difficult, particularly in patients whose samples are tested in more than 1 laboratory. This variability in results can be traced to

the differing sensitivities of the thromboplastin reagents produced by different manufacturers to coagulation factor deficiencies. To overcome this interlaboratory variation, the international normalized ratio (INR) was introduced. The INR is a mathematical conversion of a patient's PT that accounts for the sensitivity of the thromboplastin used in a given laboratory by factoring in the international sensitivity index (ISI) value supplied by its manufacturer. The INR is calculated as follows:  $INR = (patient\ PT/MNPT)^{ISI}$ , in which MNPT is the geometric mean of the PT of at least 20 healthy subjects of both sexes tested at the performing laboratory. Since its introduction, INR has reduced the interlaboratory variations in PT results.

Both PT and APTT reagents have various sensitivities to different clotting factor levels. In general, PT reagents are more sensitive to deficiencies of factor VII within the extrinsic pathway and less sensitive to deficiencies within the final common pathway (factors V, X, and II and fibrinogen).

Unfractionated heparin and low-molecular-weight heparin exert their anticoagulant effect by antithrombin-mediated inhibition of thrombin (factor II) in the final common pathway (Figure 2). Thus, in addition to prolonging the APTT, heparin in theory would prolong the PT, precluding

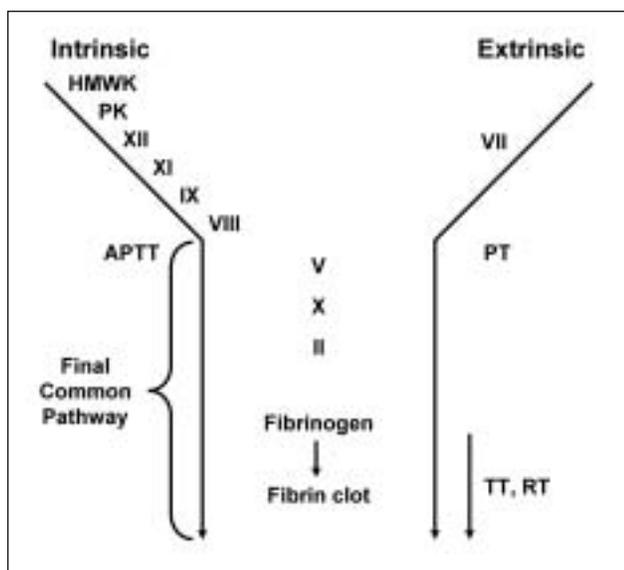


FIGURE 2. Schematic of coagulation cascade. Factors II, VII, IX, and X are vitamin K-dependent factors. APTT = activated partial thromboplastin time; HMWK = high-molecular-weight kininogen; PK = prekallikrein; PT = prothrombin time; RT = reptilase time; TT = thrombin time.

accurate monitoring of the transition to warfarin. However, this effect is overcome with the addition of heparin neutralizers (eg, Polybrene). Added to PT reagents, they can neutralize up to 2 U/mL of heparin. However, the presence of excess heparin (eg, a sample collected shortly after a heparin bolus, through a heparin-coated catheter, or above the

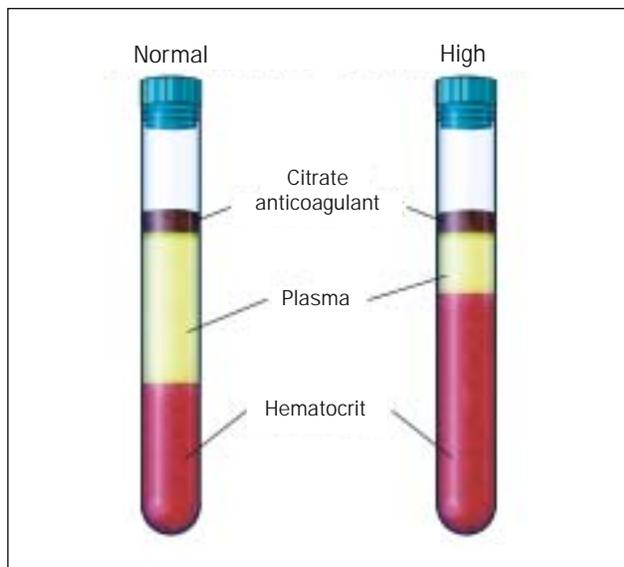


FIGURE 3. Schematic showing effect of hematocrit on relative volume of citrate anticoagulant in blood collection tube.

site of heparin infusion) may overwhelm the heparin neutralizer and prolong the PT.

#### ACTIVATED PARTIAL THROMBOPLASTIN TIME

The APTT is a measure of the integrity of the intrinsic and final common pathways of the coagulation cascade. The APTT represents the time, in seconds, for patient plasma to clot after the addition of phospholipid, an intrinsic pathway activator, and calcium. The APTT reagent is called partial thromboplastin because tissue factor is not present in conjunction with the phospholipid as it is in the PT reagent<sup>3</sup> (Figure 1). Thus, deficiencies or inhibitors of clotting factors within the intrinsic and final common pathways result in prolongation of the APTT (Figure 2).

#### DETERMINATION OF THE NORMAL (REFERENCE) RANGE

The normal or reference range for PT and APTT assays varies depending on the reagent and instrument combinations each laboratory uses. Thus, laboratories need to establish their own reference ranges by measuring the PT and APTT on plasma from healthy volunteers.<sup>4</sup> At Mayo Clinic, at least 50 healthy volunteer donors are tested to establish the reference range. Separate reference ranges need to be established for adults and children.<sup>5</sup>

#### PRETEST VARIABLES COMMONLY AFFECTING PT AND APTT

A prolonged PT or APTT, regardless of current or previous bleeding symptoms, warrants further investigation, especially when the patient is not receiving anticoagulant therapy or is not known to have liver disease. An unexpectedly prolonged PT or APTT often correctly prompts physicians to consider artifactual causes of abnormal test results. Certain pretest variables can cause artifactual prolongation of the PT or APTT (or both).

#### PATIENT HEMATOCRIT

The anticoagulant (3.2% trisodium citrate) present in the PT/APTT collection tubes chelates calcium, preventing activation of the coagulation system. The volume of the anticoagulant in the collection tubes, approximately 0.5 mL,<sup>6</sup> is intended to result in a final ratio of whole blood to anticoagulant of 9:1 and a ratio of plasma to anticoagulant of 5:1 in patients with typical hematocrits (35%-50%) (Figure 3). The hematocrit is high in blood from patients who have erythrocytosis (eg, patients with cyanotic congenital heart disease or myeloproliferative disease). When the hematocrit is high, the volume of plasma collected at venipuncture is proportionately reduced and the volume of anticoagulant increased (dilution effect). As a result, the availability of assay-added calcium is decreased, resulting

in an artifactual prolongation of the clotting time. Similar problems can occur when less than the recommended volume of blood is collected.<sup>7</sup> Alerting the laboratory about a high hematocrit and adjusting the volume of anticoagulant in the collection tube for patients with hematocrits of more than 55% will yield more reliable results.<sup>8</sup> Blood collection tubes containing the appropriate amounts of anticoagulant to accommodate different hematocrits cannot be purchased. Thus, anticoagulant adjustment is accomplished by manual addition of the appropriate amount of anticoagulant into glass collection tubes.

#### CONCENTRATION OF CITRATE ANTICOAGULANT

Because variation in the concentration of citrate anticoagulant in collection tubes (3.2% or 3.8%) affects results, a more uniform practice of collecting blood in 3.2% citrate has been recommended.<sup>6,8</sup>

#### FASTING STATE OF THE PATIENT

Before the introduction of contemporary instruments, the end point of fibrin clot detection in the PT and APTT assays consisted of manual visualization of clot formation. Currently, most laboratory instruments detect clot formation with automated photo-optical detection systems that record changes in light transmittance. However, plasma turbidity can interfere with instruments' optical systems and cause artifactual results, as it does in nonfasting, lipemic plasma specimens and in hemolyzed or icteric specimens.

#### TIME INTERVAL BETWEEN SPECIMEN COLLECTION AND ASSAY PERFORMANCE

A considerable lapse of time between blood collection and assay performance can result in artifactual results. The PT has been shown to be stable at room temperature for up to 24 hours after collection, but the APTT should be run within 4 hours, especially if the sample is heparinized.<sup>9</sup> Longer time intervals result in artifactual prolonged APTTs because factor VIII is labile.

#### EFFECTS OF THE CLINICIAN ON PRETEST VARIABLES

Busy practicing clinicians have little or no control over several of the pretest variables and specimen handling. However, they can adequately instruct patients on the importance of fasting and optimize the results of coagulation testing by alerting laboratory personnel about increased hematocrit (>55%). Before embarking on a complex investigation of a prolonged PT or APTT, clinicians should consider repeating the testing to exclude artifactual results. After appropriate sample collection, it is the coagulation laboratory's responsibility to perform the assays promptly to avoid artifactual results.<sup>9</sup>

## STEPS IN INTERPRETING AND PURSUING PROLONGED PT OR APTT RESULTS

The ordering of a PT or APTT by a physician or health care professional presupposes that a detailed history (including detailed documentation of prescription and nonprescription medications) has been obtained and that a thorough physical examination has been performed. Occasionally, when test results are abnormal, additional focused history and examination are warranted, and laboratory test results are frequently obtained before a patient encounter (eg, routine preoperative coagulation testing). For purposes of this discussion, we review the approach to laboratory evaluation of an abnormally prolonged PT or APTT and provide clinical correlative information.

### STEP 1—IS THE PT OR APTT ARTIFACTUALLY PROLONGED?

The first step in pursuing a prolonged PT or APTT is to exclude artifactual results. Typically, test results for lipemic, icteric, or hemolyzed plasma samples are accompanied by a comment from the laboratory, which should prompt consideration of retesting in the fasting state or collection of a fresh sample with careful venipuncture. However, even in the absence of specimen lipemia or an elevated hematocrit, repeating the clotting time test would not be unreasonable if results were unexpectedly prolonged, given the additional variables affecting test results that are beyond the control of the ordering physician (Figure 4).

### STEP 2—IS THE PATIENT RECEIVING ANTICOAGULANTS (VITAMIN K ANTAGONISTS, HEPARIN, OR DIRECT THROMBIN INHIBITOR)?

Therapeutic or surreptitious use of vitamin K antagonists (eg, warfarin) results in prolongation of the PT and mild prolongation of the APTT (typically, <35-40 seconds). Therapeutic intravenous administration of unfractionated heparin or its presence within central venous or arterial catheters, through which the sample may have been collected, results in a prolonged APTT. Subcutaneous administration of therapeutic doses of low-molecular-weight heparins occasionally results in a prolonged APTT; however, it is rare for the APTT to be prolonged to more than 40 seconds. Thus, for results that appear to be disproportionately prolonged, additional testing is reasonable.

### STEP 3—IS A SYSTEMIC DISEASE PROLONGING THE PT OR APTT?

After artifactual results and anticoagulants have been excluded, a detailed clinical evaluation should be undertaken (if not already performed) to detect systemic diseases that may prolong the clotting time (eg, liver disease, connective tissue disease, or disseminated intravascular coagulation and fibrinolysis) (Tables 1 and 2). In general, even in the

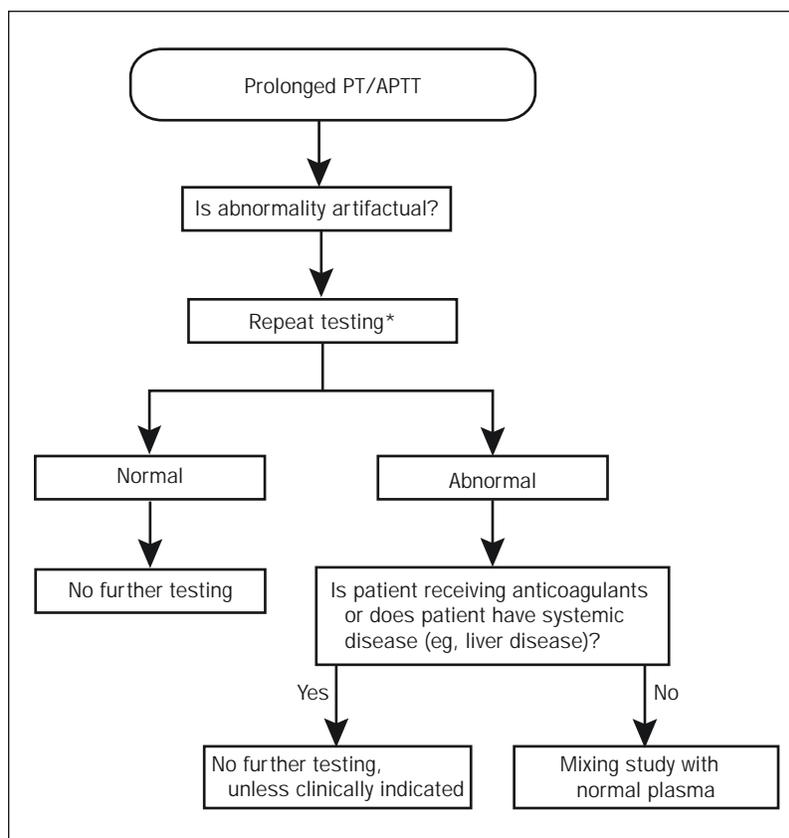


FIGURE 4. Approach to a prolonged prothrombin time (PT) or activated partial thromboplastin time (APTT)—exclusion of artifactual results. \*If original sample was collected through a central venous line or arterial line, testing should be repeated on a sample collected from peripheral venipuncture, and appropriate adjustments made if pretest variables (eg, elevated hematocrit or specimen lipemia) are suspected.

presence of a systemic disease that may explain the prolongation of the clotting time, additional testing is frequently pursued for purposes of both diagnosis and management (eg, assessing the need for and gauging the response to infusion of fresh frozen plasma or cryoprecipitate).

**STEP 4—WHAT ADDITIONAL LABORATORY TESTING SHOULD BE PURSUED?**

Staying informed about an ever-expanding repertoire of tests, in general, and the complexity of specialized coagulation testing in particular, can be a challenge for the busy health care professional. The practice in the Mayo Clinic Special Coagulation Laboratory has been to offer coagulation profiles that are based on the specific clinical question. Thus, for a prolonged PT and/or APTT, a special coagulation profile, termed the Prolonged Clotting Time Profile, is available for patients at Mayo Clinic and, through Mayo Medical Laboratories, for patients seeing their local health care professional. This profile involves performance of

screening tests (PT, APTT, and thrombin time [TT]) with mixing studies of the respective prolonged clotting times, as well as additional reflexive testing (eg, clotting factor assays and inhibitor assays), when warranted by the results of the initial findings and patient clinical history (if available) (Figure 5). Thus, it is the responsibility of the laboratory to attempt to answer the question rather than to expect the health care professional to order individual tests to determine the cause of the prolonged clotting time.

**STEP 5—HOW SHOULD A MIXING STUDY WITH NORMAL PLASMA BE INTERPRETED?**

A mixing study with normal plasma may help explain the cause of a prolonged PT and/or APTT by differentiating between a coagulation factor deficiency and the presence of an inhibitor. In such a study, the patient’s plasma is mixed with normal pooled plasma in a 1:1 ratio, and the clotting time test (PT or APTT) is repeated. One of 2 outcomes is possible: (1) correction of the clotting time (ie,

TABLE 1. Causes of Congenital Coagulation Factor Deficiencies\*

Congenital coagulation factor deficiency	Deficient factor	PT	APTT	Prevalence	Mode of inheritance
Hemophilia A	Factor VIII	Normal	Prolonged	1:5000†	X-linked recessive
Hemophilia B	Factor IX	Normal	Prolonged	1:30,000†	X-linked recessive
Hemophilia C	Factor XI	Normal	Prolonged	Up to 4%‡	Autosomal
von Willebrand disease	von Willebrand factor	Normal	Normal/prolonged	Up to 1%	Autosomal
Factor VII		Prolonged	Normal	1:500,000	Autosomal
Rare coagulation factor deficiencies					
Factor V		Prolonged	Prolonged	1:1 million	Autosomal
Factor II		Prolonged	Normal/prolonged	Rare§	Autosomal
Factor X		Prolonged	Normal/prolonged	1:500,000	Autosomal
Factor XIII		Normal	Normal	Rare§	Autosomal
Combined factors VIII and V		Prolonged	Prolonged	Rare§	Autosomal

\*APTT = activated partial thromboplastin time; PT = prothrombin time.  
 †Live male births.  
 ‡Among Ashkenazi Jews.  
 §Case reports.

the clotting time shortens into the reference range) or (2) inhibition of the clotting time (ie, it shortens, but not enough to be within the reference range).

Correction of the clotting time implies a clotting factor deficiency in 1 or more pathways (intrinsic, extrinsic, or final common pathway) (Figure 2). An inhibition of the clotting time implies that 1 or more factors or pathways are affected by an inhibitor. In general, inhibitors are classified into 3 broad categories: (1) medications (eg, heparins and direct thrombin inhibitors); (2) inhibitors directed against specific clotting factors, termed specific factor inhibitors (eg, factor VIII or factor V inhibitors); and (3) nonspecific inhibitors (eg, lupus anticoagulants [LACs], which are antibodies directed against protein-phospholipid complexes) (Figure 5).

Thereafter, pursuit of additional testing depends on factors such as the patient's clinical history and medication use. For patients with bleeding symptoms, clotting factor assays should be performed. For asymptomatic patients or those with a history of thrombosis, testing for LAC is reasonable. However, such clinical information is not always available to a reference laboratory; thus, in our laboratory, all samples are tested for the presence of heparin or a direct thrombin inhibitor, and initial testing is focused on detection of LAC with reflexive testing of coagulation factors if needed.

### APPROACH TO A PROLONGED APTT

#### APTT CORRECTS

If the prolonged APTT corrects to normal when a mixing study is performed, a coagulation factor deficiency is suggested. In the setting of a normal PT, a deficiency is im-

plied in 1 or more factors in the intrinsic pathway (ie, factors VIII, IX, XI, or XII; high-molecular-weight kininogen [HMWK]; or prekallikrein [PK]) (Figure 2). Clotting factor assays should be performed for factors VIII, IX, XI, and XII to identify the deficiency, determine whether it poses a bleeding risk to the patient, and determine whether it is congenital or acquired.

Although a prolonged APTT commonly raises concern of a bleeding disorder, severe deficiencies of factor XII, HMWK, and PK, which may result in a marked prolongation of the APTT, do *not* result in bleeding disorders. Although assays for HMWK and PK are available in selected reference laboratories, they are not commonly performed. Deficiencies of factors VIII, IX, and XI, however, result in bleeding disorders of varying severity depending on the levels of individual factors.

Once the exact factor deficiency has been identified, the next step is to determine whether the deficiency is congenital or acquired (eg, hemophilia A, B, and C are congenital deficiencies of factors VIII, IX, and XI, respectively)

TABLE 2. Causes of Acquired Factor Deficiencies

Acquired coagulation factor deficiency	Deficient factor
Warfarin	Vitamin K–dependent factors
Decreased nutritional intake or malabsorption	Vitamin K–dependent factors
Liver failure	Multiple factors
Amyloidosis	Factor X
Myeloproliferative disease	Factor V
Acquired von Willebrand syndrome	von Willebrand factor and factor VIII
Disseminated intravascular coagulation and fibrinolysis	Multiple factors

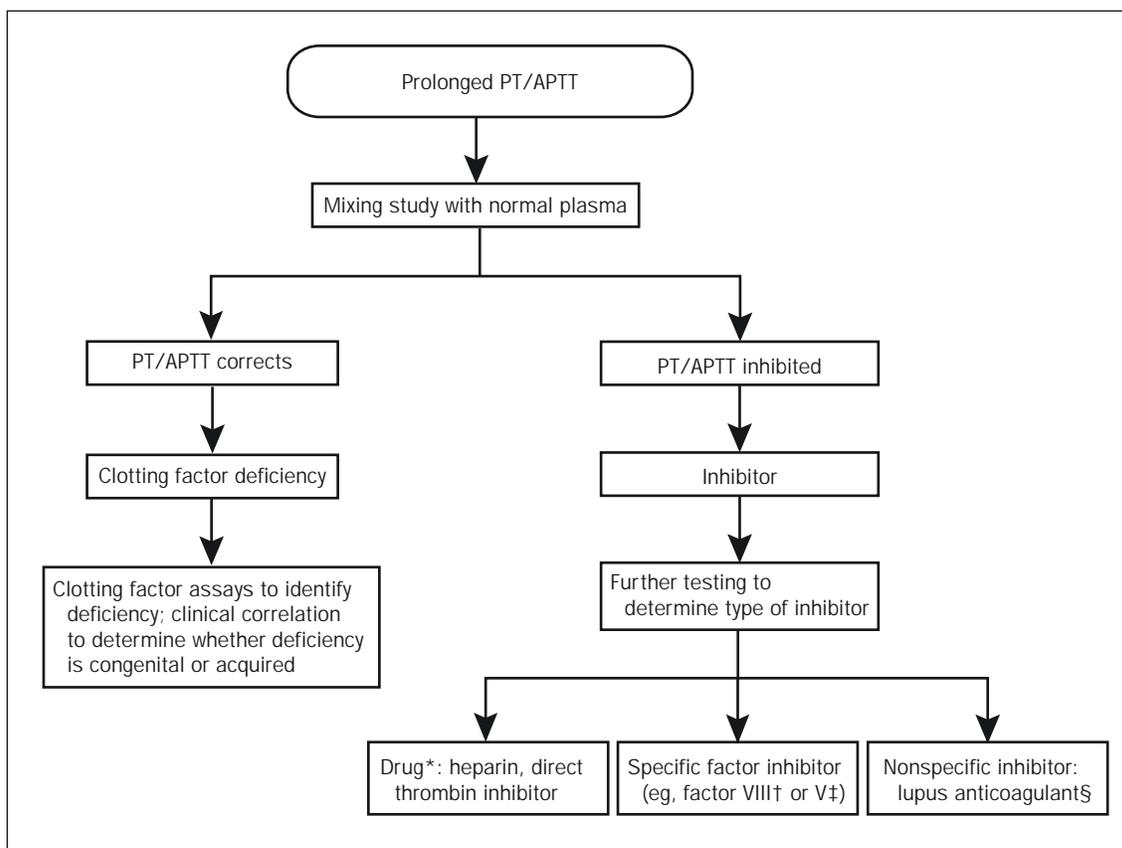


FIGURE 5. Approach to a prolonged prothrombin time (PT) or activated partial thromboplastin time (APTT)—distinguishing a clotting factor deficiency from a clotting factor inhibitor. \*Thrombin time is prolonged and reptilase time is normal; †PT is normal; ‡PT is prolonged and inhibited; §PT is typically normal but may be prolonged and inhibited when a mixing study is performed.

(Tables 1 and 2). Clinical correlation with patient personal and family history is critical to this assessment and management. Common causes of acquired factor deficiency states include warfarin use (which induces vitamin K deficiency), liver disease, or a consumptive coagulopathy such as disseminated intravascular coagulation and fibrinolysis.

**APTT Is INHIBITED**

If the APTT shortens but does not correct to normal when a mixing study is performed, then the presence of an inhibitor is suggested. If the PT is normal, then an inhibitor of the APTT assay system is suggested, including (1) drugs such as unfractionated heparin and direct thrombin inhibitors (eg, lepirudin and argatroban, both of which may also prolong and inhibit the PT), (2) LAC, and (3) specific factor inhibitor (eg, factor VIII inhibitor) (Figure 5). Thus, inhibitors are always associated with acquired disorders of the hemostatic system.

Important initial considerations are whether the inhibitor represents a risk of bleeding or a thrombosis. A review of the

patient’s medications will indicate whether heparin or a direct thrombin inhibitor is the cause of the prolonged APTT; however, occasionally, collection of the sample from a heparin-coated catheter results in a prolonged and inhibited APTT, which can cause confusion especially when the source of heparin is not obvious. In this setting, repeating the assay on a specimen collected from a peripheral vein helps clarify the cause of the prolonged APTT. Frequently, however, the clinical information on the use of anticoagulants is not available to the performing laboratory. Thus, the TT and reptilase time tests help determine whether heparin or a direct thrombin inhibitor is present. Both drugs prolong the TT but do not affect reptilase time (Figure 2). Development of autoimmune factor VIII inhibitor (acquired hemophilia) is a potentially life-threatening bleeding disorder. The rarity of this disorder may delay its diagnosis, resulting in high rates of morbidity.<sup>10</sup> In selected patients with an acquired inhibitor to factor VIII (autoimmune hemophilia), the APTT mixing study does not result in inhibition. However, after incubation for 1 hour, inhibition typically becomes apparent.

Lupus anticoagulants are antibodies directed against protein phospholipid complexes. The presence of LAC is a risk factor for thromboembolism, but patients may also be asymptomatic.<sup>11</sup> Testing for LAC consists of demonstrating prolongation and inhibition of at least 1 of 2 phospholipid-based screening tests (eg, APTT or dilute Russell viper venom test). A shortened clotting time after the addition of phospholipids (eg, platelet phospholipid for the APTT assay and phospholipid for the dilute Russell viper venom test) confirms that the inhibition of clotting time is phospholipid dependent. Finally, the effect of heparin or other inhibitors (eg, factor VIII inhibitors) should be excluded.

### APPROACH TO A PROLONGED PT

Like a prolonged APTT, a prolonged PT could reflect either a coagulation factor deficiency state or the presence of an inhibitor; thus, correction with a mixing study suggests a deficiency state, whereas inhibition suggests the presence of an inhibitor (Figure 5).

#### PT CORRECTS

For a prolonged PT that corrects when a mixing study is performed and so is suggestive of a deficiency state, we typically perform assays for factors II, V, VII, and X and for fibrinogen. When the factor deficiency is identified, clinical correlation is important for determining whether the deficiency is congenital or acquired.

Coagulation factor deficiencies that prolong the PT most commonly occur in hospitalized antibiotic-treated patients who, unable to eat, become deficient in vitamin K. Factors II, VII, IX, and X are the vitamin K–dependent procoagulant proteins that are depleted with decreased nutritional intake and more commonly with warfarin use. Given that coagulation factors are synthesized in the liver, severe liver disease results in prolongation of the PT and APTT by hampering the synthesis of coagulation factors. Factor V is low in liver disease, allowing it to be distinguished from vitamin K deficiency. Less commonly, congenital deficiency of factor VII may be discovered when the PT and APTT tests are ordered as routine preoperative tests. Rarely, evaluation of asymptomatic prolongation of the PT results in a diagnosis of isolated deficiencies of either factor X or V, both of which are rare congenital disorders. These congenital disorders should be carefully distinguished from acquired deficiencies that occur in patients with amyloidosis (factor X deficiency),<sup>12</sup> liver disease, or myeloproliferative disease (factor V deficiency).

#### PT IS INHIBITED

When the prolonged PT is inhibited rather than corrected by the mixing study, PT inhibitors are likely present. How-

ever, unlike APTT inhibitors, PT inhibitors are rarely present without prolonging and inhibiting the APTT. Inhibition of the PT can occur as a result of drugs (eg, direct thrombin inhibitor, factor V inhibitor, or excess heparin in the specimen) or, rarely, a LAC, all of which affect the APTT. The PT reagents contain a neutralizer that neutralizes up to 2 U/mL of heparin. However, specimens collected from a heparin-coated catheter, from a vein close to a site of heparin infusion, or immediately after a bolus dose of heparin may contain excess heparin that overwhelms the neutralizer and prolongs and inhibits the PT.

### APPROACH TO PROLONGATION OF BOTH PT AND APTT

Prolongation of both the PT and the APTT implies that factor deficiencies are present in the intrinsic and extrinsic pathways, in the final common pathway, or in all 3 pathways, or that inhibitors are present for both the intrinsic and the extrinsic pathways or for the final common pathway.

#### DEFICIENCIES

Deficiency states are caused by a supratherapeutic warfarin dose or anticoagulant rodenticide (brodifacoum) poisoning, which, like warfarin poisoning, results in a deficiency state of the vitamin K–dependent proteins. In patients suspected of surreptitiously consuming warfarin or brodifacoum, measurement of the respective plasma levels would confirm the cause of the apparent vitamin K–deficiency state. In addition, consumptive coagulopathies can prolong the PT and APTT.

#### INHIBITORS

Both the PT and the APTT can be inhibited by the use of direct thrombin inhibitors, by excess heparin in the sample, by potent LACs, or by nonspecific inhibitors of the PT and APTT assay systems, such as those seen in association with lymphoproliferative disorders and monoclonal protein disorders. Clinical correlation is required in the diagnosis and assessment of the hemostatic significance of these types of inhibitors.

### BLEEDING TIME

Originally introduced as a screening test for bleeding disorders, BT came to be used as a tool for routine preoperative hemostatic assessment, although data demonstrating its utility were lacking. It measures the time it takes for a standardized incision on the volar aspect of a patient's forearm to stop bleeding, thus providing an estimate of the integrity of vascular, platelet, and fibrin clot formation. A prolonged BT can result from multiple factors, including

inappropriate performance of the test by an inexperienced technologist, use of antiplatelet therapy, fragile skin, quantitative or qualitative platelet disorders, or a bleeding disorder such as von Willebrand disease. These factors reduce the sensitivity and specificity of the test. Such limitations prompted an expert panel to issue a consensus statement with the following conclusions.<sup>13</sup>

1. In the absence of the clinical history of a bleeding disorder, the BT is not a useful predictor of risk of hemorrhage with surgical procedures.
2. Normal BT does not exclude the possibility of excessive hemorrhage with invasive procedures.
3. Bleeding time cannot reliably identify patients exposed to aspirin or nonsteroidal anti-inflammatory drugs.

Efforts at Mayo Clinic to educate health care professionals about these limitations led to a more than 80% decrease in BT use during the past 3 years and to its eventual discontinuation as an orderable test.

A detailed personal and family history should be obtained, a medication review conducted, and a thorough physical examination performed when evaluating a patient with a prolonged BT. If such a clinical evaluation raises concern of a bleeding disorder, additional diagnostic evaluation should consist of screening laboratory tests and tests for the most common bleeding disorder, von Willebrand disease. Routine preoperative performance of the BT should be discouraged.

### BLEEDING DISORDERS THAT WILL NOT BE DETECTED WITH THE PT AND APTT TESTS

Because PT and APTT tests are commonly ordered in the evaluation of bleeding symptoms, it is important to recognize bleeding disorders that will not be detected by these assays. These disorders include qualitative platelet defects, which require specialized platelet function testing; von Willebrand disease, which requires assays for von Willebrand factor; factor XIII deficiency, which requires specialized factor XIII screening or functional assays; and deficiency of plasminogen activator inhibitor 1, which requires specific assays.

### REASONS FOR HEMATOLOGIST/COAGULATIONIST CONSULTATION

Primary care physicians can expedite the evaluation of a prolonged clotting time by ordering the Prolonged Clotting Time Profile. When performed by the Mayo Clinic Special Coagulation Laboratory, this profile generally results in a diagnosis. On diagnosis of congenital bleeding disorders, such as hemophilia A or B, or acquired autoimmune bleeding disorders, such as those caused by factor V or VIII inhibitor, a hematologist/coagulationist should be consulted.

Such a consultation should also be sought for patients who have clinical bleeding symptoms but whose initial screening tests are normal or nondiagnostic. However, the diagnosis of liver disease may prompt referral to a liver specialist, and the possibility of a vitamin K deficiency would prompt evaluation for nutritional intake, surreptitious ingestion of warfarin, and consideration of brodifacoum poisoning.

### CONCLUSION

Various disorders result in prolongation of the PT and APTT. Some of these disorders increase the risk of bleeding and others the risk of thrombosis, but, more importantly, selected disorders are of no hemostatic consequence. Correlation with the patient's clinical and hemostatic history is critical, and laboratory testing should be pursued especially in the absence of an obvious explanation for the prolongation of the PT or APTT. In our experience, optimal use of a laboratory is made by a profile approach, in which initial tests are followed by reflexive tests if warranted by initial findings. Results of a prolonged clotting time profile can assist in arriving at a diagnosis that will facilitate further evaluation in conjunction with a hematologist.

### REFERENCES

1. Mann KG. Biochemistry and physiology of blood coagulation. *Thromb Haemost.* 1999;82:165-174.
2. Davie EW, Fujikawa K, Kisiel W. The coagulation cascade: initiation, maintenance, and regulation. *Biochemistry.* 1991;30:10363-10370.
3. Bajaj SP, Joist JH. New insights into how blood clots: implications for the use of APTT and PT as coagulation screening tests and in monitoring of anticoagulant therapy. *Semin Thromb Hemost.* 1999;25:407-418.
4. Shahangian S, Stankovic AK, Lubin IM, Handsfield JH, White MD. Results of a survey of hospital coagulation laboratories in the United States, 2001. *Arch Pathol Lab Med.* 2005;129:47-60.
5. Andrew M, Vegh P, Johnston M, Bowker J, Ofosu F, Mitchell L. Maturation of the hemostatic system during childhood. *Blood.* 1992;80:1998-2005.
6. Adcock DM, Kressin DC, Marlar RA. Effect of 3.2% vs 3.8% sodium citrate concentration on routine coagulation testing. *Am J Clin Pathol.* 1997;107:105-110.
7. Adcock DM, Kressin DC, Marlar RA. Minimum specimen volume requirements for routine coagulation testing: dependence on citrate concentration. *Am J Clin Pathol.* 1998;109:595-599.
8. Arkin CF, Adcock DM, Ernst DJ, et al. National Committee for Clinical Laboratory Standards. *Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays: Approved Guideline—Fourth Edition.* Wayne, Pa: NCCLS; 2003. NCCLS document H21-A4.
9. Adcock D, Kressin D, Marlar RA. The effect of time and temperature variables on routine coagulation tests. *Blood Coagul Fibrinolysis.* 1998;9:463-470.
10. Pruthi RK, Nichols WL. Autoimmune factor VIII inhibitors. *Curr Opin Hematol.* 1999;6:314-322.
11. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite anti-phospholipid syndrome (APS). *J Thromb Haemost.* 2006;4:295-306.
12. Gertz MA, Kyle RA. Primary systemic amyloidosis: a diagnostic primer. *Mayo Clin Proc.* 1989;64:1505-1519.
13. Peterson P, Hayes TE, Arkin CF, et al. The preoperative bleeding time test lacks clinical benefit: College of American Pathologists' and American Society of Clinical Pathologists' position article. *Arch Surg.* 1998;133:134-139.

## Questions About Prolonged PT, APTT, and BT in Adults

1. A 45-year-old man with a history of cyanotic congenital heart disease has had multiple hemostatically uneventful surgical corrective procedures in the past. Currently, he is being evaluated for coronary angiography. He states that he has no bleeding symptoms, and physical examination shows no bruises or petechiae. He is receiving no anticoagulant medications. Laboratory data are as follows:

Test	Result	Reference range
Hemoglobin (g/dL)	20.0	12.0-15.5
Hematocrit (%)	60.0	34.9-44.5
PT (s)	18.0	8.4-12.0
APTT (s)	45.0	21.0-33.0

Which *one* of the following is the *most likely* explanation for the prolongation of the PT and APTT?

- Coagulation factor deficiency
  - Presence of a coagulation factor inhibitor
  - Artificial effect due to increased hematocrit
  - Presence of LAC
  - Factor XIII deficiency
2. A 68-year-old man needs to be evaluated before undergoing resection of an enlarged prostate gland. Which *one* of the following is the *best* initial preoperative assessment of hemostasis?
- Ordering a complete blood cell count
  - Ordering a complete blood cell count and PT
  - Ordering a complete blood cell count, PT, and APTT
  - Obtaining a detailed personal and family history of bleeding symptoms
  - Ordering a BT test
3. An 18-year-old man is evaluated for bleeding after wisdom tooth extraction. He has never had surgery and has not been circumcised. A maternal uncle died of bleeding complications after surgery, and another maternal uncle has been told that he has a bleeding disorder. The patient's mother has no bleeding symptoms. The values of a complete blood cell count and PT are normal, but the APTT is prolonged at 45 seconds (reference range, 23-33 seconds). Which *one* of the following conditions does this patient *most likely* have?
- von Willebrand disease
  - Congenital hemophilia A
  - Congenital hemophilia C
  - Congenital factor XIII deficiency
  - Congenital factor VII deficiency
4. A 26-year-old woman is evaluated who has experienced 4 consecutive spontaneous abortions in the past 2 years. She now presents to the emergency department with spontaneous swelling of and pain in her right leg. Ultrasonography confirms the presence of right superficial femoral deep venous thrombosis. Before the initiation of heparin therapy, baseline laboratory data show a normal complete blood cell count and PT. The APTT was prolonged at 68 seconds (reference range, 23-33 seconds) and was inhibited when a mixing study with normal plasma was performed. Which *one* of the following is the *most likely* reason for prolongation of the APTT?
- Presence of LAC
  - Presence of an autoimmune factor VIII inhibitor
  - Deficiency of a coagulation factor
  - Severe deficiency of factor VII
  - Heparin effect on the APTT
5. A 30-year-old woman with no previous personal or family history of a bleeding disorder experiences excessive bleeding after dental extraction. She is taking as many as 6 tablets of ibuprofen daily for pain. Laboratory data show a normal complete blood cell count and PT and an APTT of 60 seconds (reference range, 23-33 seconds). A mixing study with normal plasma corrects the APTT, and additional factor assays demonstrate normal factors VIII, IX, and XI but a low factor XII (2%; reference range, 60%-160%). Which *one* of the following is the *most likely* explanation for her bleeding?
- Excessive use of ibuprofen
  - Factor XII deficiency
  - Deficiency of HMWK
  - Deficiency of prekallikrein
  - LAC

Correct answers:

1. c, 2. d, 3. b, 4. a, 5. a